Endometrial lining in assistive reproductive technology: how thin is too thin?

This year, Louise Brown celebrates her 44th birthday. Since the birth of the first in vitro fertilization (IVF) baby, there has been monumental progress in our field, including improvements in the techniques for stimulating ovarian follicles, retrieving oocytes, culturing fertilized eggs, and testing embryo biopsies. For example, the laparoscopic approach to oocyte retrieval, pioneered by gynecologist Patrick Steptoe, is now obsolete, and a transvaginal ultrasound-guided approach is the standard of care. Fertilization rates, especially in patients with severe male factor infertility, have increased with the innovation of intracytoplasmic sperm injection. The development of sequential culture media, coupled with changes in culture conditions, has increased both the blastocyst utilization and singleton live birth rates. In recognition of the significant impact made by the development of human IVF, British physiologist Robert Edwards received the Nobel prize in medicine in 2010.

In a significant number of assisted reproductive technology cycles; however, the transfer of euploid embryos still does not result in implantation. This highlights a gap in our knowledge regarding the receptivity of the human endometrium. In the past decade, there have been some advances in our understanding of the molecular signature indicative of endometrial receptivity during the window of implantation. Similarly, there is increasing information on the morphological assessment of the preovulatory endometrium and its potential impact on assisted reproductive technology outcomes. Success rates in both the fresh and frozen embryo transfers appear to be low when the endometrial thickness is <6–7 mm, but most of these studies were unable to identify a discriminatory cut-off to recommend the cancellation of embryo transfer.

Standardization of the morphological assessment of the endometrium is an essential step to both decrease the inter-operator variability and effectively compare studies evaluating the impact of preovulatory endometrial thickness and pattern on IVF outcomes. One of the earliest consensus opinions to standardize the ultrasonographic description of the endometrium was published by the International Endometrial Tumor Analysis group formed at the World Congress of Ultrasound in Obstetrics and Gynecology in 2008 (1). On the basis of this publication, endometrial thickness should be measured perpendicular to the median longitudinal plane of the uterus as the maximum distance between the endometrial-myometrial interfaces of the uterus. The group also described a classification system for endometrial patterns based on the echogenicity of the endometrium, endometrial midline, and endometrial-myometrial junction. The endometrium is more hypoechoic relative to the myometrium in the proliferative phase, thereby exhibiting a triple-line pattern with a central hyperechoic line surrounded by two hypoechoic layers.

How often do we see a thin endometrial lining? In a meta-analysis with 10,724 patients undergoing IVF, a thin endometrium (≤7 mm) was reported in 2.4% of the women (2). In more recent studies, it was reported in 5.5%–6% of women (3). In a number of patients with a preovulatory thin endometrial lining, there is no identifiable etiology. After menstruation, endometrial repair and reepithelialization are influenced by chemokines and growth factors, such as activin, vascular endothelial growth factor, cysteine-rich secretory protein 3, and galectin-7 (4). Different signaling pathways (e.g., Wnt signaling) allow both epithelial cells and mesenchymal stem and progenitor cells to stimulate glandular and stromal regeneration. In the follicular phase, under the influence of estrogen, the endometrium develops a superficial functionalis zone (upper two-thirds) and a deeper basalis layer (lower one-third). Risk factors, such as repeated uterine surgeries and infections leading to uterine scarring, can damage the underlying population of epithelial and mesenchymal stem cells. For example, in Asherman syndrome, the endometrial stroma is largely replaced by fibrous tissue, and the glands are usually nonresponsive to steroid hormones. Depending on the etiology of the thin endometrium and the extent of damage, therapies that provide cytokines and growth factors, improve the uterine blood flow, increase tissue levels of estrogen or administer adult stem cells into the subendometrial zone might have beneficial effects.

It is clear that implantation and clinical pregnancy rates are lower in patients with a thin endometrium, and there is mounting evidence that they are at an increased risk of obstetric complications, such as pregnancy loss, preterm delivery, placenta previa, and hypertensive disorders. How can we best manage these patients? The ESHRE guidelines do not suggest frequent monitoring of endometrial thickness during ovarian stimulation. Instead, the guidelines recommend performing a single measurement of the endometrium on the day of trigger or oocyte pick-up to counsel patients on the potential for a lower pregnancy rate (5). In clomiphene citrate-associated thin lining, it is common practice to prescribe an alternative oral or injectable ovulation induction agent in a subsequent cycle. However, for the small proportion of patients with persistent thin endometrial stripe and no identifiable etiology, is it reasonable to consider some of the above-described interventions to improve the endometrial thickness?

Our patients often receive "add-on" treatments. Although grounded in science, some of these treatments have not been tested by gold standard clinical trials. The Fertile debate that follows explores the evidence for current treatment strategies for improving the endometrial lining. The low prevalence of a persistent thin endometrium poses challenges in designing studies for the recruitment of adequate patients to examine the impact of interventions on outcomes such as live birth. Moreover, because endometrial thickness may not be an independent predictor of live birth, the investigators examine how best to counsel patients regarding therapies not yet proven to improve the endometrial lining.

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A.D. has nothing to disclose.

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https://doi.org/10.1016/j.fertnstert.2022.05.032

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